Caffeine Hydrate *(BANM)*

Cafeína monohidrato; Caféine monohydratée; Caffeine Monohydrate; Coffeinum monohydricum; Kofeiinimonohydraatti; Kofein monohydrát; Kofeinas monohidratas; Koffein-monohidrát; Koffeinmonohydrat.

Кофеин Моногидрат

$C_8H_{10}N_4O_2,H_2O$ = 212.2.
CAS — 5743-12-4.
ATC — N06BC01.
ATC Vet — QN06BC01.

Pharmacopoeias. In *Chin.*, *Eur.* (see p.vii), *Int.*, *Jpn*, *US*, and *Viet.* Some pharmacopoeias include caffeine and caffeine hydrate under one monograph.

Ph. Eur. 6.2 (Caffeine Monohydrate; Caffeine Hydrate BP 2008). A white or almost white, crystalline powder or silky white or almost white crystals. It sublimes readily. Sparingly soluble in water; freely soluble in boiling water; slightly soluble in dehydrated alcohol. It dissolves in concentrated solutions of alkali benzoates or salicylates.

USP 31 (Caffeine). It is anhydrous or contains one molecule of water of hydration. An odourless white powder or white, glistening needles, usually matted together. The hydrate is efflorescent in air. The hydrate is soluble 1 in 50 of water, 1 in 75 of alcohol, 1 in 6 of chloroform, and 1 in 600 of ether. The hydrate should be stored in airtight containers.

Stability. References to the stability of caffeine and caffeine citrate.

1. Eisenberg MG, Kang N. Stability of citrated caffeine solutions for injectable and enteral use. *Am J Hosp Pharm* 1984; **41:** 2405–6.
2. Nahata MC, *et al.* Stability of caffeine injection in intravenous admixtures and parenteral nutrition solutions. *DICP Ann Pharmacother* 1989; **23:** 466–7.
3. Hopkin C, *et al.* Stability study of caffeine citrate. *Br J Pharm Pract* 1990; **12:** 133.
4. Donnelly RF, Tirona RG. Stability of citrated caffeine injectable solution in glass vials. *Am J Hosp Pharm* 1994; **51:** 512–14.
5. Fraser BD. Stability of caffeine citrate injection in polypropylene syringes at room temperature. *Am J Health-Syst Pharm* 1997; **54:** 1106, 1108.

Adverse Effects, Treatment, and Precautions

As for Theophylline, p.1140.

Tolerance occurs rapidly to the stimulating effects of caffeine; physical signs of withdrawal including irritability, restlessness, lethargy, and headache may occur if intake is stopped abruptly.

◊ General references.

1. Wills S. Drugs and substance misuse: caffeine. *Pharm J* 1994; **252:** 822–4.
2. Fredholm BB, *et al.* Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 1999; **51:** 83–133.

Breast feeding. Studies examining the transfer of caffeine into breast milk after oral doses of 35 to 336 mg of caffeine have recorded peak maternal plasma concentrations of 2.4 to 4.7 micrograms/mL, peak maternal saliva concentrations of 1.2 to 9.2 micrograms/mL, and peak breast-milk concentrations of 1.4 to 7.2 micrograms/mL. At these concentrations in breast milk, the calculated daily caffeine ingestion by breast-fed infants ranged from 1.3 to 3.1 mg, which was not thought to present a hazard, although irritability and a poor sleeping pattern have been reported.[1-4]

The American Academy of Pediatrics[5] states that caffeine is excreted slowly by the infant and may be associated with irritability and poor sleeping pattern when ingested by breast-feeding mothers. However, no effects occur with moderate intake of caffeinated beverages (2 to 3 cups daily) and caffeine is usually compatible with breast feeding.

1. Tyrala EE, Dodson WE. Caffeine secretion into breast milk. *Arch Dis Child* 1979; **54:** 787–800.
2. Hildebrandt R, *et al.* Transfer of caffeine to breast milk. *Br J Clin Pharmacol* 1983; **15:** 612P.
3. Sagraves R, *et al.* Pharmacokinetics of caffeine in human breast milk after a single oral dose of caffeine. *Drug Intell Clin Pharm* 1984; **18:** 507.
4. Berlin CM, *et al.* Disposition of dietary caffeine in milk, saliva, and plasma of lactating women. *Pediatrics* 1984; **73:** 59–63.
5. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 19/03/08)

Effects on the cardiovascular system. An increased caffeine intake has been associated with an increase in daytime blood pressure.[1] The study, in 82 healthy, normotensive adolescents, suggested that caffeine consumption may be a factor contributing to essential hypertension in young people.

High dose caffeine (25 mg/kg) used as a loading dose in the prevention and treatment of neonatal apnoea (see p.1118) resulted in a marked reduction of cerebral and intestinal blood flow velocity in preterm infants;[2] no changes were noted in left ventricular output, blood pressure, or heart rate. The authors attributed the effect on blood flow velocity to vasoconstriction, and suggested a smaller caffeine loading dose, repeated several hours later. A later study, also in preterm infants, which examined the effect of a divided loading dose of caffeine (12.5 mg/kg repeated after 4 hours), found that cerebral blood flow velocity was decreased after the second dose; intestinal blood flow velocity and left ventricular output remained unchanged.[3] The authors concluded that the 20% reduction in cerebral blood flow velocity observed was probably not meaningful for infants with adequate cerebral oxygen supply; however, an infant's ability to respond to hypoxaemia by vasodilatation may be compromised.

For a discussion of the effects of caffeine-containing beverages on cardiovascular risk factors, see p.2415.

1. Savoca MR, *et al.* Association of ambulatory blood pressure and dietary caffeine in adolescents. *Am J Hypertens* 2005; **18:** 116–20.
2. Hoecker C, *et al.* Caffeine impairs cerebral and intestinal blood flow velocity in preterm infants. *Pediatrics* 2002; **109:** 784–7.
3. Hoecker C, *et al.* Effects of a divided high loading dose of caffeine on circulatory variables in preterm infants. *Arch Dis Child Fetal Neonatal Ed* 2006; **91:** F61–F64.

Effects on mental function. A report of 6 cases of excessive daytime sleepiness associated with high caffeine intake.[1]

1. Regestein QR. Pathologic sleepiness induced by caffeine. *Am J Med* 1989; **87:** 586–8.

Headache. Headache is a recognised symptom of caffeine withdrawal and even subjects who drink moderate amounts of coffee can develop headaches lasting 1 to 6 days when switched to a decaffeinated brand.[1] It has also been suggested that postoperative headache could be attributed to caffeine withdrawal as fasting patients are required to abstain from drinking tea or coffee before surgical procedures. Several studies[2-4] have found a positive association between postoperative headache and daily caffeine consumption, although there have also been negative findings.[5] A prospective study suggested that a prophylactic intravenous dose of caffeine on the day of surgery reduced the likelihood of postoperative headache in patients at risk of caffeine withdrawal.[6]

In a case-control study,[7] investigating the possible association of dietary and medicinal caffeine use with chronic daily headache (CDH), caffeine was found to be a modest risk factor for CDH onset, regardless of headache type. Patients suffering from CDH were more likely overall to have been high caffeine consumers before the onset of CDH; no association was found with current caffeine consumption.

1. van Dusseldorp M, Katan MB. Headache caused by caffeine withdrawal among moderate coffee drinkers switched from ordinary to decaffeinated coffee: a 12 week double blind trial. *BMJ* 1990; **300:** 1558–9.
2. Galletly DC, *et al.* Does caffeine withdrawal contribute to postanaesthetic morbidity? *Lancet* 1989; **i:** 1335.
3. Weber JG, *et al.* Perioperative ingestion of caffeine and postoperative headache. *Mayo Clin Proc* 1993; **68:** 842–5.
4. Nikolajsen L, *et al.* Effect of previous frequency of headache, duration of fasting and caffeine abstinence on perioperative headache. *Br J Anaesth* 1994; **72:** 295–7.
5. Verhoeff FH, Millar JM. Does caffeine contribute to postoperative morbidity? *Lancet* 1990; **336:** 632.
6. Weber JG, *et al.* Prophylactic intravenous administration of caffeine and recovery after ambulatory surgical procedures. *Mayo Clin Proc* 1997; **72:** 621–6.
7. Scher AI, *et al.* Caffeine as a risk factor for chronic daily headache: a population-based study. *Neurology* 2004; **63:** 2022–7.

Overdosage. Reports and reviews of caffeine toxicity.

1. Zimmerman PM, *et al.* Caffeine intoxication: a near fatality. *Ann Emerg Med* 1985; **14:** 1227–9.
2. Dalvi RR. Acute and chronic toxicity of caffeine: a review. *Vet Hum Toxicol* 1986; **28:** 144–50.
3. Rivenes SM, *et al.* Intentional caffeine poisoning in an infant. *Pediatrics* 1997; **99:** 736–8.
4. Anderson BJ, *et al.* Caffeine overdose in a premature infant: clinical course and pharmacokinetics. *Anaesth Intensive Care* 1999; **27:** 307–11.
5. Ergenekon E, *et al.* Caffeine intoxication in a premature neonate. *Paediatr Anaesth* 2001; **11:** 737–9.
6. Holstege CP, *et al.* Massive caffeine overdose requiring vasopressin infusion and hemodialysis. *J Toxicol Clin Toxicol* 2003; **41:** 1003–7.

Pregnancy. In the USA, the FDA has advised pregnant women to limit their intake of caffeine and caffeine-containing beverages to a minimum, but this recommendation was based largely on *animal* studies and the effect of caffeine on the human fetus and fetal loss during pregnancy is controversial.[1] Although some studies found no evidence that moderate caffeine use increased the risk of spontaneous abortion,[2,3] others have reported conflicting results.[4,5] There is some evidence for an effect on fetal growth, but again it is not clear that this applies generally: a prospective population-based study in the UK found that a decreased birth-weight with increased caffeine intake was only significant in smokers.[6] The authors of this study concurred that a reduction in caffeine intake during pregnancy would be prudent, together with stopping smoking. An association between high maternal caffeine intake during pregnancy and an increased risk of the sudden infant death syndrome has also been reported,[7] although another study found no such association.[8]

1. Eskenazi B. Caffeine during pregnancy: grounds for concern? *JAMA* 1993; **270;** 2973–4.
2. Mills JL, *et al.* Moderate caffeine use and the risk of spontaneous abortion and intrauterine growth retardation. *JAMA* 1993; **269:** 593–7.
3. Klebanoff MA, *et al.* Maternal serum paraxanthine, a caffeine metabolite, and the risk of spontaneous abortion. *N Engl J Med* 1999; **341:** 1639–44.
4. Infante-Rivard C, *et al.* Fetal loss associated with caffeine intake before and during pregnancy. *JAMA* 1993; **270:** 2940–3.
5. Cnattingius S, *et al.* Caffeine intake and the risk of first-trimester spontaneous abortion. *N Engl J Med* 2000; **343:** 1839–45.
6. Cook DG, *et al.* Relation of caffeine intake and blood caffeine concentrations during pregnancy to fetal growth: prospective population based study. *BMJ* 1996; **313:** 1358–62.
7. Ford RPK, *et al.* Heavy caffeine intake in pregnancy and sudden infant death syndrome. *Arch Dis Child* 1998; **78:** 9–13.
8. Alm B, *et al.* Caffeine and alcohol as risk factors for sudden infant death syndrome. *Arch Dis Child* 1999; **81:** 107–11.

Interactions

Like theophylline (see p.1142) caffeine undergoes extensive metabolism by hepatic microsomal cytochrome P450 isoenzyme CYP1A2, and is subject to numerous interactions with other drugs and substances which enhance or reduce its metabolic clearance.

◊ Reviews.

1. Carrillo JA, Benitez J. Clinically significant pharmacokinetic interactions between dietary caffeine and medications. *Clin Pharmacokinet* 2000; **39:** 127–53.

Alcohol. In a study of 8 healthy subjects given an oral dose of alcohol of 2.2 mL/kg, caffeine 150 mg by mouth did not antagonise the central effects of alcohol and, instead, a synergistic interaction occurred which further increased reaction time. The common practice of drinking coffee after drinking alcohol in order to sober up is not supported by these results.[1] Another study[2] found that some antagonism of the central effects of alcohol was produced by caffeine, although there was no reversal of subjective sensations of drunkenness; however the dose of caffeine in this study (400 mg) was considerably higher.

1. Oborne DJ, Rogers Y. Interactions of alcohol and caffeine on human reaction time. *Aviat Space Environ Med* 1983; **54:** 528–34.
2. Azcona O, *et al.* Evaluation of the central effects of alcohol and caffeine interaction. *Br J Clin Pharmacol* 1995; **40:** 393–400.

Antiarrhythmics. In 7 healthy subjects and 5 patients with cardiac arrhythmias, *mexiletine* in a single dose of 200 mg and a dose of 600 mg daily respectively, reduced the elimination of caffeine by 30 to 50%.[1] *Lidocaine*, *flecainide*, and *tocainide* had no effect on caffeine elimination in healthy subjects.[1]

1. Joeres R, Richter E. Mexiletine and caffeine elimination. *N Engl J Med* 1987; **317:** 117.

Antibacterials. Caffeine elimination half-life has been reported to be increased and clearance decreased when given with *ciprofloxacin*,[1-3] *enoxacin*,[2,3] and *pipemidic acid*,[2,3] whereas *lomefloxacin*,[4] *norfloxacin*,[2,3] and *ofloxacin*[2,3] had little or no effect on these parameters. Enoxacin had the greatest inhibitory effect on caffeine clearance.[2,3]

1. Healy DP, *et al.* Interaction between oral ciprofloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1989; **33:** 474–8.
2. Harder S, *et al.* Ciprofloxacin-caffeine: a drug interaction established using in vivo and in vitro investigations. *Am J Med* 1989; **87** (suppl 5A): 89–91S.
3. Barnett G, *et al.* Pharmacokinetic determination of relative potency of quinolone inhibition of caffeine disposition. *Eur J Clin Pharmacol* 1990; **39:** 63–9.
4. Healy DP, *et al.* Lack of interaction between lomefloxacin and caffeine in normal volunteers. *Antimicrob Agents Chemother* 1991; **35:** 660–4.

Antidepressants. Fluvoxamine has been reported to significantly reduce the clearance and prolong the elimination half-life of caffeine.[1] The clinical importance of this interaction, attributed to inhibition of cytochrome P450 isoenzyme CYP1A2 by fluvoxamine, remains to be established.

1. Culm-Merdek KE, *et al.* Fluvoxamine impairs single-dose caffeine clearance without altering caffeine pharmacodynamics. *Br J Clin Pharmacol* 2005; **60:** 486–93.

Antiepileptics. The mean clearance of caffeine was increased and its half-life decreased in epileptic patients taking *phenytoin* compared with healthy controls, resulting in lower plasma-caffeine concentrations. Treatment with *carbamazepine* or *valproic acid* had no effect on the pharmacokinetics of caffeine.[1]

1. Wietholtz H, *et al.* Effects of phenytoin, carbamazepine, and valproic acid on caffeine metabolism. *Eur J Clin Pharmacol* 1989; **36:** 401–6.

Antifungals. In a single-dose study in healthy subjects, *terbinafine* 500 mg by mouth decreased the clearance and increased the elimination half-life of caffeine 3 mg/kg given intravenously. *Ketoconazole* 400 mg by mouth did not prolong the elimination of caffeine to a significant extent.[1]

1. Wahlländer A, Paumgartner G. Effect of ketoconazole and terbinafine on the pharmacokinetics of caffeine in healthy volunteers. *Eur J Clin Pharmacol* 1989; **37:** 279–83.

Antigout drugs. In a study in 2 healthy subjects, the plasma half-life of caffeine was essentially unchanged by 7 days of treatment with *allopurinol* 300 mg or 600 mg daily by mouth. However, allopurinol caused a specific, dose-dependent inhibition of the conversion of 1-methylxanthine to 1-methyluric acid.[1]

1. Grant DM, *et al.* Effect of allopurinol on caffeine disposition in man. *Br J Clin Pharmacol* 1986; **21:** 454–8.

Gastrointestinal drugs. *Cimetidine* 1 g daily by mouth reduced the systemic clearance of caffeine and prolonged its elimination half-life in 5 healthy subjects. Although the steady-state plasma-caffeine concentration would increase by about 70%, it was thought unlikely that this would produce adverse clinical effects.[1] However, in contrast a study in 11 children given cimetidine in doses of 11 to 36 mg/kg daily for gastritis found no evidence that it altered the metabolism of a dose of ^{13}C-labelled caffeine.[2]

1. Broughton LJ, Rogers HJ. Decreased systemic clearance of caffeine due to cimetidine. *Br J Clin Pharmacol* 1981; **12:** 155–9.
2. Parker AC, *et al.* Lack of inhibitory effect of cimetidine on caffeine metabolism in children using the caffeine breath test. *Br J Clin Pharmacol* 1997; **43:** 467–70.

Lithium. For mention of the effect of caffeine on serum-lithium concentrations, see Xanthines, p.405.

Methoxsalen. Single oral doses of 1.2 mg/kg methoxsalen have reduced the clearance of caffeine in patients with psoriasis,[1,2] consistent with a cytochrome P450 isoenzyme CYP1A2-dependent inhibition of caffeine demethylation.[2]

1. Mays DC, *et al.* Methoxsalen is a potent inhibitor of the metabolism of caffeine in humans. *Clin Pharmacol Ther* 1987; **42:** 621–6.
2. Bendriss EK, *et al.* Inhibition of caffeine metabolism by 5-methoxypsoralen in patients with psoriasis. *Br J Clin Pharmacol* 1996; **41:** 421–4.

Sex hormones. The clearance of caffeine has been reported to be reduced and its elimination half-life increased in women taking *oral contraceptives*.[1-3] This interaction was thought to be due to impairment of hepatic metabolism of caffeine by sex hormones and could result in increased accumulation of caffeine. Similar results have been reported[4] in a study of postmenopausal women given oestrogens for *hormone replacement therapy* and caffeine.

1. Patwardhan RV, *et al.* Impaired elimination of caffeine by oral contraceptive steroids. *J Lab Clin Med* 1980; **95:** 603–8.
2. Abernethy DR, Todd EL. Impairment of caffeine clearance by chronic use of low-dose oestrogen-containing oral contraceptives. *Eur J Clin Pharmacol* 1985; **28:** 425–8.
3. Balogh A, *et al.* Influence of ethinylestradiol-containing combination oral contraceptives with gestodene or levonorgestrel on caffeine elimination. *Eur J Clin Pharmacol* 1995; **48:** 161–6.
4. Pollock BG, *et al.* Inhibition of caffeine metabolism by estrogen replacement therapy in postmenopausal women. *J Clin Pharmacol* 1999; **39:** 936–40.

Sympathomimetics. Use of caffeine 400 mg with *phenylpropanolamine* 75 mg, both given orally as modified-release preparations, produced greater plasma-caffeine concentrations in healthy subjects than caffeine alone. Greater increases in blood pressure and more reports of physical adverse effects occurred after the combination than after either drug alone.[1]

Giving caffeine with *ephedrine* has been reported to produce significant cardiovascular, metabolic, and hormonal responses, including increased systolic blood pressure and heart rate, and raised fasting glucose and insulin.[2] These enhanced effects appear to be the result of a pharmacodynamic rather than a pharmacokinetic interaction, and led to the issue of a warning by Health Canada in 2006 not to use weight loss products containing both caffeine and ephedrine, since the combination had caused reported adverse effects ranging from dizziness, tremors, headaches, and irregularities in heart rate to seizures, psychosis, heart attacks, and stroke.[3] Those particularly at risk include individuals suffering from ischaemic heart disease, hypertension, and diabetes.[2,3]

1. Lake CR, *et al.* Phenylpropanolamine increases plasma caffeine levels. *Clin Pharmacol Ther* 1990; **47:** 675–85.
2. Haller CA, *et al.* Enhanced stimulant and metabolic effects of combined ephedrine and caffeine. *Clin Pharmacol Ther* 2004; **75:** 259–73.
3. Health Canada. Health Canada advises consumers not to use weight loss products containing ephedrine and caffeine (issued 23rd May 2006). Available at: http://www.hc-sc.gc.ca/ahc-asc/media/advisories-avis/_2006/2006_33-eng.php (accessed 09/07/08)

Theophylline. For the effect of caffeine on the metabolism and elimination of theophylline, see p.1144.

Pharmacokinetics

Caffeine is absorbed readily after oral doses and is widely distributed throughout the body. It is also absorbed through the skin. Absorption when given rectally by suppository may be slow and erratic. Absorption after intramuscular injection may be slower than after oral doses. Caffeine passes readily into the CNS and into saliva; low concentrations are also present in breast milk. Caffeine crosses the placenta.

In adults, caffeine is metabolised almost completely in the liver via oxidation, demethylation, and acetylation, and is excreted in the urine as 1-methyluric acid, 1-methylxanthine, 7-methylxanthine, 1,7-dimethylxanthine (paraxanthine), 5-acetylamino-6-formylamino-3-methyluracil (AFMU), and other metabolites with only about 1% unchanged. Hepatic cytochrome P450 isoenzyme CYP1A2 is involved in caffeine enzymatic metabolism. Neonates have a greatly reduced capacity to metabolise caffeine, due to their immature hepatic enzyme systems, and it is largely excreted unchanged in the urine. By 9 months of age, urinary excretion is similar to that seen in adults. Elimination half-lives are about 3 to 7 hours in adults but may be about 3 to 4 days in neonates.

Metabolism and excretion. The metabolism of caffeine has been shown to be dose dependent[1,2] with clearance decreasing as the dose is increased suggesting saturable metabolism. Four- to fivefold differences in plasma half-lives of caffeine are common among healthy people. The plasma half-life of caffeine is decreased by smoking[3] and by exercise,[4] and is increased by liver disease such as cirrhosis and viral hepatitis,[3,5] and in pregnancy.[3] The plasma half-life of caffeine is not affected by old age[6] or obesity.[7] Drug interactions also affect the pharmacokinetics of caffeine (see above).

1. Cheng WSC, *et al.* Dose-dependent pharmacokinetics of caffeine in humans: relevance as a test of quantitative liver function. *Clin Pharmacol Ther* 1990; **47:** 516–24.
2. Denaro CP, *et al.* Dose-dependency of caffeine metabolism with repeated dosing. *Clin Pharmacol Ther* 1990; **48:** 277–85.
3. Kalow W. Variability of caffeine metabolism in humans. *Arzneimittelforschung* 1985; **35:** 319–24.
4. Collomp K, *et al.* Effects of moderate exercise on the pharmacokinetics of caffeine. *Eur J Clin Pharmacol* 1991; **40:** 279–82.
5. Scott NR, *et al.* The pharmacokinetics of caffeine and its dimethylxanthine metabolites in patients with chronic liver disease. *Br J Clin Pharmacol* 1989; **27:** 205–13.
6. Blanchard J, Sawers SJA. Comparative pharmacokinetics of caffeine in young and elderly men. *J Pharmacokinet Biopharm* 1983; **11:** 109–26.
7. Abernethy DR, *et al.* Caffeine disposition in obesity. *Br J Clin Pharmacol* 1985; **20:** 61–6.

Uses and Administration

Caffeine is a methylxanthine that, like theophylline (p.1146), inhibits the enzyme phosphodiesterase and has an antagonistic effect at central adenosine receptors. It is a stimulant of the CNS, particularly the higher centres, and it can produce a condition of wakefulness and increased mental activity. It may also stimulate the respiratory centre, increasing the rate and depth of respiration. Its bronchodilating properties are weaker than those of theophylline. Caffeine facilitates the performance of muscular work and increases the total work that can be performed by a muscle. The diuretic action of caffeine is weaker than that of theophylline.

Caffeine is used as a mild CNS stimulant in usual oral doses of 50 to 100 mg, although doses of up to 200 mg may be used. Doses should not be taken more often than every 3 hours. It is also frequently included in oral analgesic preparations with aspirin, paracetamol, or codeine in unit doses of about 15 to 65 mg but its clinical benefit is debated (see Pain, below). Caffeine is sometimes given with ergotamine in preparations for the treatment of migraine, usually in unit doses of 100 mg. Caffeine citrate has been used similarly. For details of doses in children, see Administration in Children, below.

Caffeine and sodium benzoate and caffeine and sodium salicylate are readily soluble in water and have been used when caffeine is to be given by injection.

Beverages of coffee, tea, and cola provide active doses of caffeine (see p.2415).

◊ General references.

1. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; **49:** 37–50.

Administration in children. Caffeine is used in the short-term treatment of neonatal apnoea of prematurity (below). An initial loading dose of caffeine citrate is 20 mg/kg (equivalent to 10 mg/kg caffeine), followed by a maintenance dose of caffeine citrate 5 mg/kg daily. These doses may be given either orally or by intravenous infusion. Serum concentrations of caffeine should be measured before starting treatment in infants who have already been treated with theophylline (which is metabolised to caffeine in infants) or whose mothers consumed caffeine before delivery; serious toxicity has been associated with serum concentrations greater than 50 micrograms/mL.

Asthma. Caffeine's bronchodilating activity is about 40% that of theophylline[1] and oral doses of 5 or 10 mg/kg have been shown to produce an effect.[2,3] Because of its weak action other xanthines are generally recommended in asthma (p.1108), but it may need to be avoided before tests of lung function.[4]

1. Gong H, *et al.* Bronchodilator effects of caffeine in coffee: a dose-response study of asthmatic subjects. *Chest* 1986; **89:** 335–42.
2. Becker AB, *et al.* The bronchodilator effects and pharmacokinetics of caffeine in asthma. *N Engl J Med* 1984; **310:** 743–6.
3. Bukowskyj M, Nakatsu K. The bronchodilator effect of caffeine in adult asthmatics. *Am Rev Respir Dis* 1987; **135:** 173–5.
4. Bara AI, Barley EA. Caffeine for asthma. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 19/03/08).

Dementia. A cohort study in 7017 patients aged 65 years and over examined the association between caffeine intake, cognitive decline, and incident dementia.[1] Caffeine consumption itself was found to be significantly associated with a wide range of variables also associated with cognitive decline, such as age, gender, depressive symptoms, and cardiovascular disease. Although no relationship was found between baseline caffeine intake and incident dementia in a 4-year follow-up period, caffeine consumption appeared to reduce cognitive decline in women without dementia. The authors concluded that further studies are required to ascertain whether caffeine may be of value in prolonging the period of mild cognitive impairment in women before a diagnosis of dementia.

1. Ritchie K, *et al.* The neuroprotective effects of caffeine: a prospective population study (the Three City Study). *Neurology* 2007; **69:** 536–45.

Diabetes mellitus. A single dose of caffeine 250 mg proved beneficial in augmenting warning symptoms and physiological responses to experimentally-induced hypoglycaemia in diabetic patients,[1] and was suggested as a potentially useful adjunct for diabetics who have difficulty in recognising the onset of hypoglycaemia (see Diabetic Emergencies, p.435). In a subsequent placebo-controlled crossover study oral caffeine 200 mg twice daily appeared to enhance the intensity of hypoglycaemic warning symptoms in patients with type 1 diabetes on a low-caffeine diet.[2] A later study[3] reported an association between caffeine and a reduction in the frequency of nocturnal hypoglycaemia in patients with type 1 diabetes, which the authors suggested may explain the increase in warning symptoms and hormonal responses previously reported in daytime hypoglycaemia. Caffeine has also been seen to impair postprandial glucose metabolism in patients with type 2 diabetes,[4] raising concern about the potential hazards of caffeine in these patients for whom decreases in insulin sensitivity might increase average glucose levels and the risk of diabetic complications.

1. Debrah K, *et al.* Effect of caffeine on recognition of and physiological responses to hypoglycaemia in insulin-dependent diabetes. *Lancet* 1996; **347:** 19–24.
2. Watson JM, *et al.* Influence of caffeine on the frequency and perception of hypoglycemia in free-living patients with type 1 diabetes. *Diabetes Care* 2000; **23:** 455–9.
3. Richardson T, *et al.* Influence of caffeine on frequency of hypoglycaemia detected by continuous interstitial glucose monitoring system in patients with long-standing type 1 diabetes. *Diabetes Care* 2005; **28:** 1316–20.
4. Lane JD, *et al.* Caffeine impairs glucose metabolism in type 2 diabetes. *Diabetes Care* 2004; **27:** 2047–8.

Diagnosis and testing. Caffeine excretion assessed by measuring its urinary metabolites or by the exhalation of labelled CO_2 in breath after doses of ^{13}C- or ^{14}C-labelled caffeine has been used to develop liver function tests and to determine the activity of specific enzymes such as xanthine oxidase, P450 cytochromes, and polymorphic *N*-acetyltransferase.[1]

Caffeine given orally has been used to assess acetylator status by determining the metabolic ratio of the metabolites 5-acetylamino-6-formylamino-1-methyluracil (AFMU) to 1-methylxanthine in urine,[2] but some have questioned its value.[3]

Caffeine has also been investigated in the diagnosis of susceptibility to malignant hyperthermia.[4] Intramuscular injection induced a temporary hypermetabolic reaction in subjects susceptible to malignant hyperthermia, but not in non-susceptible subjects or healthy controls. The authors suggested that monitoring of carbon dioxide, produced by hypermetabolism, might offer a minimally invasive test for such susceptibility.

1. Kalow W, Tang B-K. The use of caffeine for enzyme assays: a critical appraisal. *Clin Pharmacol Ther* 1993; **53:** 503–14.
2. Hildebrand M, Seifert W. Determination of acetylator phenotype in caucasians with caffeine. *Eur J Clin Pharmacol* 1989; **37:** 525–6.
3. Notarianni LJ, *et al.* Caffeine as a metabolic probe: NAT2 phenotyping. *Br J Clin Pharmacol* 1996; **41:** 169–73.
4. Anetseder M, *et al.* Diagnosis of susceptibility to malignant hyperthermia by use of a metabolic test. *Lancet* 2002; **359:** 1579–80.

ECT. In patients whose seizure duration is declining despite maximal ECT stimulation, pretreatment with high-dose intravenous caffeine increases seizure duration without affecting seizure threshold. Theophylline has been used similarly, see p.1142.

References.

1. Hinkle PE, *et al.* Use of caffeine to lengthen seizures in ECT. *Am J Psychiatry* 1987; **144:** 1143–8.
2. Coffey CE, *et al.* Caffeine augmentation of ECT. *Am J Psychiatry* 1990; **147:** 579–85.
3. Kelsey MC, Grossberg GT. Safety and efficacy of caffeine-augmented ECT in elderly depressives: a retrospective study. *J Geriatr Psychiatry Neurol* 1995; **8:** 168–72.

Neonatal apnoea. Apnoea of infancy has been defined as cessation of breathing either lasting 20 seconds or more or associated with bradycardia, cyanosis, pallor, and marked hypotonia, for which no specific cause can be identified.[1] Premature infants

(less than 37 weeks of gestation) can exhibit periodic breathing with pathological apnoea (apnoea of prematurity); this usually resolves as the infant approaches term and the neurological systems controlling ventilation mature.[1,2]

The management of neonatal apnoea for which no underlying disorder can be found may involve supportive measures such as cardiorespiratory monitoring;[1] continuous positive airways pressure and drug therapy may be required.[3]

The methylxanthines, aminophylline, theophylline, and caffeine, reduce the frequency of apnoea and the need for mechanical ventilation in preterm infants during the first seven days of therapy.[4] In preterm infants given intermittent positive airway pressure, prophylactic methylxanthine treatment increases the chances of successful extubation within one week.[5] There is evidence to suggest that this benefit might be more helpful in infants of extremely low birth-weight extubated in the first week. High doses of caffeine, 20 mg/kg daily, have been used around the time of extubation in neonates born at less than 30 weeks of gestation. Short term benefits were noted,[6] and no evidence of harm in the first year of life. Caffeine has also been reported to reduce the incidence of bronchopulmonary dysplasia in infants with very low birth-weight,[3] so that positive airways pressure could be stopped earlier in infants given caffeine compared with those given placebo. A later evaluation of these infants found that caffeine therapy improved the rate of survival without neurodevelopmental disability at 18 to 21 months.[7] The incidence of cerebral palsy and cognitive delay were also reduced. Earlier stopping of positive airway pressure in the infants assigned to caffeine explained almost half of the beneficial long-term effect of caffeine, but further studies are required to ascertain other potential mechanisms of action. Caffeine has a wider therapeutic index, fewer peripheral adverse effects than theophylline, and a longer half-life enabling once-daily dosage, and is therefore preferred.[4,8] Caffeine is given as the citrate salt. It is well absorbed when given orally; intravenous treatment is rarely necessary. For details of doses, see Administration in Children, above. The *BNFC* considers appropriate serum concentrations in neonatal apnoea to be 8 to 12 micrograms/mL for theophylline and 10 to 20 micrograms/mL for caffeine. Higher caffeine concentrations of 25 to 35 micrograms/mL may sometimes be required. Previous treatment with theophylline, infants born to mothers who consumed caffeine before delivery, infants showing signs of toxicity, or infants who require higher doses will require monitoring of plasma caffeine concentrations; however, routine monitoring of plasma concentrations is not always considered necessary.[9] During the first year of life, the elimination half-life of both caffeine and theophylline decreases significantly as the infant matures; regular monitoring of serum concentrations and constant dosage adjustments are therefore required if therapy is prolonged.[1]

For details of the adverse effects on the cardiovascular system associated with caffeine during treatment of neonatal apnoea, see Effects on the Cardiovascular System, above.

Use of doxapram may be considered for apnoea that does not respond to xanthine therapy.[1,2,10] It is reported to be similar in effect to the methylxanthines, and may also be of benefit as an addition to xanthine therapy.[11,12] Doxapram is poorly absorbed orally and adverse effects such as hypertension, CNS stimulation, and heart block have been reported.[13]

1. Kriter KE, Blanchard J. Management of apnea in infants. *Clin Pharm* 1989; **8:** 577–87.
2. Ruggins NR. Pathophysiology of apnoea in preterm infants. *Arch Dis Child* 1991; **66:** 70–73.
3. Schmidt B, *et al.* Caffeine therapy for apnea of prematurity. *N Engl J Med* 2006; **354:** 2112–21.
4. Henderson-Smart DJ, Steer P. Methylxanthine treatment for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2001 (accessed 19/03/08).
5. Henderson-Smart DJ, Davis PG. Prophylactic methylxanthines for extubation in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2003 (accessed 19/03/08).
6. Steer P, *et al.* High dose caffeine citrate for extubation of preterm infants: a randomised controlled trial. *Arch Dis Child Fetal Neonatal Ed* 2004; **89:** F499–F503.
7. Schmidt B, *et al.* Long-term effects of caffeine therapy for apnea of prematurity. *N Engl J Med* 2007; **357:** 1893–1902.
8. Steer PA, Henderson-Smart DJ. Caffeine versus theophylline for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 1998 (accessed 19/03/08).
9. Natarajan G, *et al.* Therapeutic drug monitoring for caffeine in preterm neonates: an unnecessary exercise? *Pediatrics* 2007; **119:** 936–40.
10. Hascoet J-M, *et al.* Risks and benefits of therapies for apnoea in premature infants. *Drug Safety* 2000; **23:** 363–79.
11. Eyal F, *et al.* Aminophylline versus doxapram in idiopathic apnea of prematurity: a double-blind controlled study. *Pediatrics* 1985; **75:** 709–13.
12. Peliowski A, Finer NN. A blinded, randomized, placebo-controlled trial to compare theophylline and doxapram for the treatment of apnea of prematurity. *J Pediatr* 1990; **116:** 648–53.
13. Henderson-Smart DJ, Steer P. Doxapram versus methylxanthine for apnea in preterm infants. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2000 (accessed 19/03/08).

Obesity. A 1999 review[1] of non-prescription weight loss supplements concluded that controlled studies have not shown fat loss in overweight individuals using caffeine without an energy-restricted diet. A later study[2] examined a herbal combination product, containing amongst its active ingredients caffeine (from kola nut) and ephedrine (from ephedra), in the treatment of overweight and obesity without other lifestyle modifications. Some beneficial effects on body-weight were reported after 12 weeks of treatment compared with placebo; however, although no serious adverse effects were seen in the healthy subjects enrolled in this study, the herbal product used contained relatively low amounts of active ingredients compared with preparations used in other similar studies. The FDA has since banned the sale of dietary supplements containing ephedra as they present an unreasonable risk to health (see Ephedra, p.1558), and concerns have been raised about potential additive stimulant effects of preparations containing both caffeine and ephedrine, see Sympathomimetics under Interactions, above.

1. Egger G, *et al.* The effectiveness of popular, non-prescription weight loss supplements. *Med J Aust* 1999; **171:** 604–8.
2. Coffey CS, *et al.* A randomized double-blind placebo-controlled clinical trial of a product containing ephedrine, caffeine, and other ingredients from herbal sources for treatment of overweight and obesity in the absence of lifestyle treatment. *Int J Obes Relat Metab Disord* 2004; **28:** 1411–19.

Orthostatic hypotension. Caffeine has been of benefit in the treatment of orthostatic hypotension (p.1530) due to autonomic failure in some patients, especially for postprandial hypotension.[1-3] However, efficacy has only been shown in mild cases and it is usually ineffective in severe cases.[4]

1. Onrot J, *et al.* Hemodynamic and humoral effects of caffeine in autonomic failure. *N Engl J Med* 1985; **313:** 549–54.
2. Hoeldtke RD, *et al.* Treatment of orthostatic hypotension with dihydroergotamine and caffeine. *Ann Intern Med* 1986; **105:** 168–73.
3. Tonkin AL. Postural hypotension. *Med J Aust* 1995; **162:** 436–8.
4. Mathias CJ. Orthostatic hypotension. *Prescribers' J* 1995; **35:** 124–32.

Pain. Caffeine has been widely used in analgesic preparations to enhance the effects of both non-opioid and opioid analgesics but is of debatable benefit (see under Choice of Analgesic, p.2). Some investigators have failed to show that caffeine offers any benefit[1,2] but others have shown that the adjuvant use of caffeine can increase analgesic activity.[3-8] A meta-analysis of 10 studies comparing paracetamol plus caffeine with paracetamol alone in women with postpartum uterine cramp found any benefit of the combination to be minimal.[9] A literature review[10] concluded that there was some evidence that caffeine may be useful as an analgesic adjuvant in relieving headache, but that the dose may need to be at least 65 mg and that these higher doses increase the risk of nervousness and dizziness. Evidence for the effects of caffeine in other types of pain, such as postpartum, postoperative, dental, rheumatic, and cancer pain, was inconclusive.

In the UK it is generally recommended that caffeine-containing analgesic preparations should not be used not only because of doubts about caffeine enhancing the analgesic effect but because it can add to gastrointestinal adverse effects and in large doses can itself cause headache.

Whether caffeine enhances the gastrointestinal absorption of ergotamine in preparations for the relief of migraine is not clear.

1. Winter L, *et al.* A double-blind, comparative evaluation of acetaminophen, caffeine, and the combination of acetaminophen and caffeine in outpatients with post-operative oral surgery pain. *Curr Ther Res* 1983; **33:** 115–22.
2. Sawynok J. Pharmacological rationale for the clinical use of caffeine. *Drugs* 1995; **49:** 37–50.
3. Laska EM, *et al.* Caffeine as an analgesic adjuvant. *JAMA* 1984; **251:** 1711–18.
4. Rubin A, Winter L. A double-blind randomized study of an aspirin/caffeine combination versus acetaminophen/aspirin combination versus acetaminophen versus placebo in patients with moderate to severe post-partum pain. *J Int Med Res* 1984; **12:** 338–45.
5. Schachtel BP, *et al.* Caffeine as an analgesic adjuvant: a double-blind study comparing aspirin with caffeine to aspirin and placebo in patients with sore throat. *Arch Intern Med* 1991; **151:** 733–7.
6. Migliardi JR, *et al.* Caffeine as an analgesic adjuvant in tension headache. *Clin Pharmacol Ther* 1994; **56:** 576–86.
7. Kraetsch HG, *et al.* Analgesic effects of propyphenazone in comparison to its combination with caffeine. *Eur J Clin Pharmacol* 1996; **49:** 377–82.
8. Diener HC, *et al.* The fixed combination of acetylsalicylic acid, paracetamol and caffeine is more effective than single substances and dual combination for the treatment of headache: a multicentre, randomized, double-blind, single-dose, placebo-controlled parallel group study. *Cephalalgia* 2005; **25:** 776–87.
9. Zhang WY, Li Wan Po A. Analgesic efficacy of paracetamol and its combination with codeine and caffeine in surgical pain—a meta-analysis. *J Clin Pharm Ther* 1996; **21:** 261–82.
10. Zhang W-Y. A benefit-risk assessment of caffeine as an analgesic adjuvant. *Drug Safety* 2001; **24:** 1127–42.

POST-DURAL PUNCTURE HEADACHE. Intravenous caffeine sodium benzoate may relieve post-dural puncture headache (p.1851) that persists despite conservative therapy.

Psoriasis. The efficacy of a 10% formulation of topical caffeine in the treatment of psoriasis has been investigated in a group of 39 patients with stable plaque psoriasis.[1] Improvements were seen at each 2-week follow-up stage, but the difference only became significant after 8 weeks. The only adverse effect noted during the study was mild itching, reported by 2 of the caffeine recipients.

1. Vali A, *et al.* Evaluation of the efficacy of topical caffeine in the treatment of psoriasis vulgaris. *J Dermatol Treat* 2005; **16:** 234–7.

Preparations

BP 2008: Aspirin and Caffeine Tablets; Caffeine Citrate Injection; Caffeine Citrate Oral Solution;
USP 31: Acetaminophen and Caffeine Tablets; Acetaminophen, Aspirin, and Caffeine Tablets; Butalbital, Acetaminophen, and Caffeine Capsules; Butalbital, Acetaminophen, and Caffeine Tablets; Butalbital, Aspirin, and Caffeine Capsules; Butalbital, Aspirin, and Caffeine Tablets; Butalbital, Aspirin, Caffeine, and Codeine Phosphate Capsules; Caffeine and Sodium Benzoate Injection; Caffeine Citrate Injection; Caffeine Citrate Oral Solution; Ergotamine Tartrate and Caffeine Suppositories; Ergotamine Tartrate and Caffeine Tablets; Propoxyphene Hydrochloride, Aspirin, and Caffeine Capsules.

Proprietary Preparations (details are given in Part 3)
Arg.: Guarana; Percutafeine; ***Austria:*** Coffekapton; ***Braz.:*** Percutafeine†; ***Canad.:*** Wake-Up Tablets; ***Chile:*** Asafen Nueva Formula†; Jaquedryl; ***Cz.:*** Kinedryl; ***Fin.:*** Cofi-Tabs; ***Fr.:*** Percutafeine; ***Ger.:*** Percoffedrinol N†; ***Gr.:*** Cafcit; ***Irl.:*** Pro-Plus; ***Mex.:*** Ifa Kafen†; Kafen†; ***Pol.:*** Kofex; ***Port.:*** Bioregime SlimKit†; ***Rus.:*** Vasobral (Вазобрал); ***Spain:*** Durvitan; ***UK:*** Pro-Plus; ***USA:*** Cafcit; Caffedrine; Enerjets; Keep Alert; Lucidex; NoDoz; Stay Alert; Vivarin.

Multi-ingredient: numerous preparations are listed in Part 3.

Choline Theophyllinate *(BAN, rINN)*

Choline, Théophyllinate de; Cholini Theophyllinas; Koliiniteofyllinaatti; Kolinteofyllinat; Oxtriphylline; Teofilinato de colina; Theophylline Cholinate.

Холина Теофиллинат

$C_{12}H_{21}N_5O_3$ = 283.3.
CAS — 4499-40-5.
ATC — R03DA02.
ATC Vet — QR03DA02.

Pharmacopoeias. In *Br.*, *Chin.*, and *US*.
BP 2008 (Choline Theophyllinate). A white crystalline powder, odourless or with a faint amine-like odour. It contains between 41.9% and 43.6% of choline and between 61.7% and 65.5% of theophylline, each calculated with reference to the dried substance. Very soluble in water; soluble in alcohol; very slightly soluble in chloroform and in ether. Store at a temperature not exceeding 25°. Protect from light.
USP 31 (Oxtriphylline). A white crystalline powder, having an amine-like odour. It contains not less than 61.7% and not more than 65.5% of anhydrous theophylline. Soluble 1 in 1 of water; freely soluble in alcohol; very slightly soluble in chloroform. A 1% solution in water has a pH of about 10.3. Store in airtight containers.

Profile
Choline theophyllinate is a theophylline salt that liberates theophylline (p.1140) in the body; choline theophyllinate 1.57 mg is equivalent in theophylline content to about 1 mg of anhydrous theophylline. It is used as a bronchodilator for reversible airways obstruction. The usual oral maintenance dose for adults is 800 mg daily, in 4 divided doses. The daily dose should be adjusted according to clinical response and serum-theophylline concentrations (see Uses and Administration of Theophylline, p.1146). For details of doses in children see Administration in children, below.

Administration in children. Choline theophyllinate can be given to children in oral doses of 10 to 20 mg/kg daily, in 3 or 4 divided doses.

Preparations
BP 2008: Choline Theophyllinate Tablets;
USP 31: Oxtriphylline Delayed-release Tablets; Oxtriphylline Extended-release Tablets; Oxtriphylline Oral Solution; Oxtriphylline Tablets.

Proprietary Preparations (details are given in Part 3)
Austral.: Brondecon Elixir; ***Canad.:*** Choledyl; ***Ger.:*** Euspirax†; ***Gr.:*** Choledyl; ***Swed.:*** Teovent; ***USA:*** Choledyl†.

Multi-ingredient: ***Austral.:*** Brondecon Expectorant; ***Canad.:*** Choledyl Expectorant; ***NZ:*** Broncelix; Brondecon; Pharmacycare Cough Expectorant†; ***Port.:*** Vitasma†.

Cilomilast *(USAN, rINN)*

Cilomilastum; SB-207499. *cis*-4-Cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexanecarboxylic acid.

Циломиласт

$C_{20}H_{25}NO_4$ = 343.4.
CAS — 153259-65-5.